MEDICAL PROCEEDINGS

MEDIESE BYDRAES

A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

P.O. Box 1010 · Johannesburg | Posbus 1010 · Johannesburg

Editor : Redakteur

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Vol. 7 | 11 March 1961 Maart 11 | No. 5

EDITORIAL · REDAKSIONEEL

AN ORAL CONTRACEPTIVE

AMENDING THE HORMONES

'N MONDELINGE VOORBEHOEDMIDDEL

WYSIGING VAN DIE HORMONE

Hark, Nature . . .
Suspend thy purpose, if thou didst intend
To make this creature fruitful;
Into her womb convey sterility,
Dry up in her the organs of increase.

King Lear, Act 1, Scene 4 (*Folio Society Edition*, p. 37).

The physiological inhibition of ovulation during pregnancy suggests a biological approach to the problem of preventing conception.

Although a technique based on this approach has theoretically seemed feasible for some time, it has not been until recently that our knowledge of reproductive physiology has been adapted as a practical and effective measure for preventing pregnancy.

In the normal reproductive cycle, the oestrogenic phase (associated with the development of the follicle) is followed at about the midpoint of the menstrual cycle by ovulation and the development of the corpus luteum, when a progestational hormone is produced resulting in a preparation of the endometrial bed for the reception of the fertilized ovum. In the absence of a fertilized ovum, the endometrial lining is shed, i.e. normal menstruation occurs. It is interesting that the full effect of the progestational hormone during the menstrual cycle is not obtained until after there has been a preparation of the tissues by oestrogen.

Die fisiologiese inhibisie van ovulasie tydens swangerskap suggereer 'n biologiese benadering tot die probleem van die voorkoming van bevrugting.

Hoewel 'n tegniek gebaseer op hierdie benadering reeds 'n hele ruk lank as teoreties moontlik beskou is, is ons kennis van die voortplantingsfisiologie eers onlangs aangewend vir 'n praktiese en doeltreffende metode om swangerskap te voorkom.

In die normale voortplantingsiklus word die estrogeenfase (geassosieer met die ontwikkeling van die follikel) teen omtrent die middelpunt van die menstruele siklus opgevolg deur ovulasie en die ontwikkeling van die *corpus luteum*, wanneer 'n progestatiewe hormoon geproduseer word. Die gevolg hiervan is die voorbereiding van die endometrium vir die ontvangs van die bevrugte eier. In die afwesigheid van 'n bevrugte eier word die endometrium afgeskei, d.w.s. normale menstruasie vind plaas. Dit is interessant dat die volle effek van die progestatiewe hormoon gedurende die menstruele siklus eers verkry word nadat estro-

If ovulation could be inhibited by some delicate hormonal mechanism which could pinpoint this aspect of follicular activity and if, at the same time, a normal sequence in the development of the endometrium could be maintained throughout the menstrual cycle, a situation as closely approaching the normal as possible could be created and at the same time be an effective barrier to conception.

Developments in the field of reproductive physiology have long suggested that some such delicate hormonal technique for interfering with the reproductive cycle should be possible.

Against this biological background, it is not surprising to learn that a synthetic hormone has been developed which is progestational in its action and which, when acting physiologically in conjunction with an oestrogenic hormone, is able to inhibit ovulation and produce a normal physiological development of the endometrium which is shed at regular intervals as in normal menstruation.

The Research Division of an American pharmaceutical organization, G. D. Searle & Co., has produced such a synthetic progestational substance. It is known as norethynodrel* (Fig. 1). The formula bears an interesting structural family relationship to progesterone (Fig. 2). When norethynodrel acts concomitantly with an oestrogen, it can produce a progestational endometrium closely resembling the structure of the endometrium in early pregnancy. At the same time, there appears to be a selective inhibition of pituitary function resulting in the suppression of ovulation without, as far as can be determined, any apparent interference with any of the other trophic functions of the pituitary.

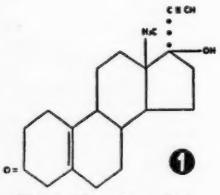

Fig. 1. Norethynodrel

Pincus *et al.*[1] have reported that norethynodrel (given in combination with an oestrogen) when administered from days 5 to 24 of a menstrual cycle, mimics the mucosal changes seen with normal ovulation, although this latter event has not occurred.

The secretory response in this steroid-treated endometrium is shorter than normal and rarely

* Dispensed in combination with an oestrogen and marketed in South Africa as Enavid.

1. Pincus, G., Garcia, C.-R., Rice-Wray, E. and Rodriguez, I. (1958): Amer. J. Obstet. Gynecol., **75**, 1333.

geen vir die voorbereiding van die weefsels gesorg het.

Indien ovulasie gestrem kan word deur die een of ander delikate meganisme wat hierdie aspek van follikulêre aktiwiteit toelig, en as 'n normale volgorde in die ontwikkeling van die endometrium terselfdertyd dwarsdeur die menstruele siklus gehandhaaf kan word, sal dit moontlik wees om 'n toestand so naby aan normaal soos moontlik te skep wat tegelykertyd ook as 'n doeltreffende versperring teen bevrugting kan dien.

Ontwikkelinge op die gebied van voortplantingsfisiologie het lank reeds gesuggereer dat so 'n delikate hormoontegniek vir die versteuring van die voortplantingsiklus moontlik behoort te wees.

Teen hierdie biologiese agtergrond is dit nie verrassend om te verneem nie dat 'n sintetiese hormoon ontwikkel is wat progestatief in sy effek is, en wat, as dit fisiologies saam met 'n estrogeenhormoon werk, in staat is om ovulasie te strem, en om 'n normale fisiologiese ontwikkeling van die endometrium wat by gereelde tussenpose afgeskei word, net soos in die geval van normale menstruasie, te produseer.

Die navorsingsafdeling van 'n Amerikaanse farmaseutiese organisasie, G. D. Searle & Co., het nou so 'n sintetiese progestatiewe stof geproduseer. Dit staan bekend as noretinodrel* (Fig. 1). Die formule toon 'n interessante struktuur-familieverwantskap met progesteroon (Fig. 2). As noretinodrel saam met estrogeen optree, produseer dit 'n progestatiewe endometrium wat 'n noue ooreenkoms met die struktuur van die endometrium tydens die vroeë stadium van swangerskap toon. Terselfdertyd skyn dit asof daar 'n selektiewe inhibisie van pituitêre funksie is met 'n gevolglike onderdrukking van ovulasie sonder, sover vasgestel kan word, enige sigbare inmenging met enigeen van die ander trofiese funksies van die hipofise.

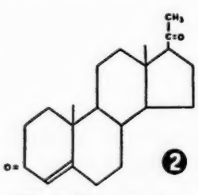

Fig. 2. Progesterone

Pincus *et al.*[1] rapporteer dat as noretinodrel saam met estrogeen vanaf die 5de tot die 24ste dag van die menstruele siklus toegedien word,

* Berei in 'n verbinding met 'n estrogeen, en in Suid-Afrika bemark as *Enavid*.

1. Pincus, G., Garcia, C.-R., Rice-Wray, E. en Rodriguez, I. (1958): Amer. J. Obstet. Gynecol., **75**, 133.

progresses to full, typical secretion by the glandular epithelium. The glands (in shape and structure) appear gradually to regress, not to the condition typical of the late proliferative stage, but to a condition suggestive of the fifth post-ovulatory day.

There is also a predecidual cytoplasmic enlargement of the stromal cells, which can so closely simulate that of early pregnancy as to mislead the unwary. (This, incidentally, emphasizes the need to furnish pathologists with adequate information when endometrial biopsies are sent from women who have been treated with this steroid).

This synthetic hormone, therefore, appears capable of producing the morphological endometrial changes associated with pseudo-pregnancy, but its action seems to be confined to this aspect of the interference with the cycle, as no other endocrine abnormalities are associated with the administration of this hormone.

There seems thus to be very sound morphological evidence to support the contention that a physiological situation can be induced whereby ovulation is inhibited, suppressing the cyclical activity of the ovary in this one limited respect. It provides, therefore, a most delicate technique for the prevention of pregnancy, if it can be assured that no undesirable or dangerous consequences result from the use of this hormone over prolonged periods of contraceptive practice.

This matter has been tested clinically very extensively in recent years. A considerable number of investigators have carried out contraceptive experiments with the voluntary cooperation of a very large number of women (by now almost 2,000 in all) over a period for close on 5 years. Although the dosage schedule was experimental, it is clear from the protocols that none of the patients became pregnant while taking norethynodrel as directed. It is important also that women on this contraceptive regime were able to interrupt the procedure, when normal pregnancies were established without any difficulty.[2]

The side effects observed in some women included pelvic pain, breast tenderness, nausea, dizziness and vomiting. These complaints diminished after the first cycle and in any event were prevented in 82% of the reactors by an antacid.[1]

It is known that sex steroids are metabolized in the liver and some of them have been known to cause liver damage. These, however, have been androgens such as methyl testosteron

2. Any Questions? (1960): Brit. Med. J., **2**, 551.

dit die slymvliesveranderings wat tydens normale ovulasie plaasvind, naboots, hoewel laasgenoemde voorval nie plaasgevind het nie.

Die afskeidingsreaksie van hierdie steroïedbehandelde endometrium is korter as normaal, en vorder selde tot volledige, tipiese afskeiding deur die klierepiteel. Wat fatsoen en struktuur betref, skyn dit asof die kliere geleidelik agteruitgaan, nie na die toestand wat tipies van die latere proliferatiewe stadium is nie, maar na 'n toestand wat 'n mens aan die vyfde na-ovulasie-dag laat dink.

Daar is ook 'n pre-desiduale sitoplasmiese vergroting van die steunweefselselle wat so 'n noue ooreenkoms met dié van vroeë swangerskap toon dat dit die onversigtige op 'n verkeerde spoor kan bring. (Dit, tussen hakies, beklemtoon die noodsaaklikheid om patoloë te voorsien van volledige inligting wanneer endometriale biopsies, afkomstig van vroue wat met hierdie steroïed behandel is, aan hulle gestuur word).

Dit skyn derhalwe asof hierdie sintetiese hormoon in staat is om die morfologiese endometriale veranderings wat met pseudoswangerskap geassosieer is, te produseer, maar dit lyk asof die effek daarvan beperk bly tot hierdie aspek van inmenging met die siklus, aangesien geen ander endokrienabnormaliteite met die toediening van hierdie hormoon geassosieer is nie.

Dit wil dus voorkom asof daar besonder gegronde morfologiese bewyse is ter ondersteuning van die bewering dat 'n fisiologiese toestand teweeggebring kan word waar ovulasie gestrem en die siklusaktiwiteit van die eierstok in hierdie enkele, beperkte opsig onderdruk word. Dit kan dus beskou word as 'n besonder delikate tegniek vir die voorkoming van swangerskap, indien daar verseker kan word dat geen onwenslike of gevaarlike gevolge sal voortspruit uit die langdurige gebruik van hierdie hormoon as voorbehoedmiddel nie.

Hierdie aangeleentheid is gedurende die afgelope paar jaar aan uitgebreide kliniese toetse onderwerp. Oor 'n tydperk van byna 5 jaar het 'n aansienlike aantal navorsingswerkers voorbehoedende proefnemings gedoen met die vrywillige medewerking van 'n besonder groot aantal vroue (teen hierdie tyd byna 2,000). Hoewel die dosisskedules van 'n proefondervindelike aard was, is dit duidelik uit die protokols dat geeneen van die pasiënte swanger geword het solank hulle noretinodrel volgens die voorskrifte geneem het nie. Van belang is ook die feit dat die vroue wat hulle aan hierdie voorbehoedende behandeling onderwerp het, in staat was om die prosedure te

rone. Liver function tests on representative groups of patients and controls have been carried out. The results indicate normal liver function where norethynodrel has been the steroid administered.[3]

One of the hazards which springs to mind with the prolonged use of a sex steroid is the possibility of inducing malignant disease, especially in the reproductive organs. The available data indicate that, in some 800 women participating in a contraceptive experiment with this hormone in Puerto Rico, and observed for a period of 4 years, only one case of carcinoma of the cervix was uncovered, whereas an anticipated 20 cases should have been uncovered in a group of this size over this period of time.

Far from introducing a hazard of malignant disease, there seems to be suggestive evidence that an opposite effect may in fact have been obtained. As Pincus[4] announced in New York: 'We must approach the suspected anti-cancer activity of the steroid hormone (norethynodrel) drugs with caution. It may take years to prove.'

No substantial information is yet available about possible effects on the breast, benign or malignant. In the New York Conference, however, it was stated that cancer of the breast appeared to be unusually infrequent among women taking the pill to prevent pregnancy. This is not a sufficient basis for establishing an anti-breast cancer activity of the hormone. It does, however, encourage the view that the regular use of this hormone over as long a period as 4 years, does not induce an increased hazard for breast cancer. Further observations on this aspect of the matter are being conducted.

The efficacy of this hormone as a contraceptive measure has come under very close scrutiny all over the world. The total weight of evidence appears to substantiate the view that norethynodrel (when used, e.g. in the form of Enavid) is a safe method of successfully preventing pregnancy. This technique of contraception does not interfere with the fertility of subject, nor does it lead to hormonal disturbances. It is also useful to note the view ex-

3. Oral Contraceptives: Statement by Medical Advisory Council (1960): Lancet, **2**, 256.

4. Pincus, G. (1960): Reported in New York at a news conference following a closed-circuit TV discussion by 8 United States medical authorities on the use of oral contraceptives.

onderbreek, en dat normale swangerskappe toe sonder die geringste moeite bewerkstellig is.[2]

Die newe-effekte wat by sommige vroue waargeneem is, sluit die volgende in: pyn in die bekken, gevoeligheid van die borste, mislikheid, duiseligheid en braking. Hierdie klagtes het na die eerste siklus afgeneem, en by 82% van die vrouens wat op hierdie wyse gereageer het, was dit in elk geval moontlik om die betrokke newe-effekte deur die toediening van 'n teensuur te voorkom.

Dit is bekend dat geslagsteroïede in die lewer gemetaboliseer word, en dis ook bekend dat sommige van hulle die lewer kan beskadig. Dit is egter androgene, soos metieltestosteroon. Lewerfunksietoetse is uitgevoer met verteenwoordigende groepe pasiënte en kontrolepersone, en die resultate dui op normale lewerfunksie waar die gebruikte steroïed noretinodrel was.[3]

Een van die gevare wat 'n mens te binne skiet as 'n geslagsteroïed oor 'n baie lang tydperk gebruik word, is die moontlikheid van kwaadaardige kwale, veral in die voortplantingsorgane. Die beskikbare gegewens bewys dat slegs een geval van servikale karsinoom ontdek is onder die ongeveer 800 vroue in Puerto Rica wat aan die voorbehoedende proefneming met hierdie hormoon deelgeneem het en oor 'n tydperk van 4 jaar waargeneem is. In 'n groep van hierdie grootte, en oor die betrokke tydperk, kan 20 gevalle van karsinoom gewoonlik verwag word.

Verre daarvan dus dat die gebruik van die middel die gevaar van kwaadaardige siekte meebring, skyn dit asof daar suggestiewe bewyse is dat net die teenoorgestelde effek verwag kan word. Soos Pincus[4] in New York gesê het:

‚Ons moet die vermoedelike anti-kankeraktiwiteit van steroïedhormoon-middels (noretinodrel) met versigtigheid benader. Jare sal miskien nodig wees om dit te bewys.'

Geen definitiewe inligting oor die moontlike goedaardige of kwaadaardige effek op die borste is tot dusver beskikbaar nie. Op die New Yorkse konferensie is daar egter verklaar dat borskanker 'n buitengewone seldsaamheid skyn te wees onder die vroue wat die pille gebruik om swangerskap te voorkom. Dit is nie voldoende getuienis vir 'n bewering dat die hormoon 'n anti-borskankeraktiwiteit besit nie. Dit sterk egter die sienswyse dat die gereelde gebruik van hierdie hormoon oor 'n tydperk van soveel soos 4 jaar geen groter gevaar van borskanker meebring nie. Verdere waarnemings oor hierdie aspek van die saak word gedoen.

2. Any Questions? (1960): Brit. Med. J., **2**, 551.

3. *Oral Contraceptives*: Verklaring deur die Mediese Adviserende Raad (1960): Lancet, **2**, 256.

4. Pincus, G. (1960): Gerapporteer in New York op 'n nuuskonferensie ná die beeldradio-uitsending, oor 'n geslote stroomkring, van 'n bespreking van die onderwerp van mondelinge voorbehoedmiddels deur 8 Amerikaanse mediese deskundiges.

pressed in the *British Medical Journal* on 19 November 1960 at page 1527:

'The published evidence that the use of norethynodrel plus ethinyloestradiol 3-methyl ether (Enavid) for oral contraception provides a substantially higher degree of protection than does any other method of which there are published data.'

As the initial studies already cover a period of some 5 years with safety, it seems clear that those who adopt this contraceptive technique now will have additional evidence after the next 5 years of the safety and efficacy of this procedure over a 10-year period. By staggering the use of this technique of contraception in this way over 5-year periods, it should be possible progressively to accumulate very reliable evidence about its safety and efficacy as time goes by, without introducing into the lives of the patients concerned any undue risk. The periodic check every 5 years of the status of the technique should provide suitable biological and clinical control.

One should not lose sight of the very important psychological and psychiatric repercussions of a contraceptive technique of this kind. Many stresses in marital situations arise directly from sex problems associated with unwanted pregnancies. A secure and safe technique of this kind must make a major contribution to the lessening of such tensions and stresses.

The economics of such a contraceptive procedure must assume considerable importance in a decision whether it should be adopted. A modest smoker of some 20 cigarettes a day, smoking regularly throughout the year, spends about twice as much as his wife would spend on this hormone as a contraceptive measure.

As our legislation stands, the provisions of the Sixth Schedule in relation to potentially harmful drugs ensure that norethynodrel will automatically fall within its provisions and will therefore not be available for sale direct to the public over the pharmacist's counter. This ensures a further protection and control in that women wishing to employ this method of contraception will, initially at all events, do so under the supervision and guidance of a medical practitioner, as it will be impossible for her to obtain the hormone without a medical prescription.

There is world-wide concern about the problem of controlling population and restricting its increase in certain parts of the world to a level commensurate with what the economy of the area can support. This hormonal technique would appear to be a very effective way of implementing such major policies on a mass scale, with a minimum of difficulty in instructing the women concerned.

Die doeltreffendheid van hierdie hormoon as 'n voorbehoedmiddel is dwarsdeur die wêreld noukeurig bestudeer. Dit skyn asof die totale gewig van getuienis die mening staaf dat noretinodrel (as dit bv. in die vorm van Enavid gebruik word) 'n veilige metode is om swangerskap op 'n suksesvolle wyse te voorkom. Hierdie voorbehoedende tegniek affekteer nie die vrugbaarheid van die pasiënt nie, en dit gee nie aanleiding tot hormoonversteurings nie. Dit is ook interessant om te let op die sienswyses wat op 19 November 1960 op bladsy 1527 van die *British Medical Journal* uitgespreek is:

‚Die gepubliseerde getuienis oor die gebruik van noretinodrel plus etinielestradiol-3-metiel-eter (Enavid) as 'n mondelinge voorbehoedmiddel bewys dat dit 'n aansienlik hoër mate van beskerming verleen as enige ander metode waaroor daar gepubliseerde gegewens bestaan.'

Aangesien die aanvanklike studies reeds 'n tydperk van ongeveer 5 veilige jare dek, is dit duidelik dat diegene wat hierdie voorbehoedtegniek toepas ná verloop van 'n verdere 5 jaar oor addisionele bewyse van die veiligheid en doeltreffendheid van die prosedure oor 'n tydperk van 10 jaar sal beskik. Deur hierdie voorbehoedende tegniek op hierdie wyse in tydperke van 5 jaar in te deel, behoort dit moontlik te wees om met verloop van tyd besonder betroubare bewyse oor die veiligheid en doeltreffendheid daarvan in te win, sonder om die lewe van die betrokke pasiënte aan enige buitensporige gevaar bloot te stel. As die status van die tegniek periodiek al om die 5 jaar nagegaan word, behoort dit geskikte biologiese en kliniese kontrole te verseker.

Die baie belangrike psigologiese en psigiatriese reperkussies van 'n voorbehoedende tegniek van hierdie aard moet ook nie uit die oog verloor word nie. Baie van die dinge wat spanning in die huwelikslewe veroorsaak, spruit regstreeks voort uit geslagsprobleme geassosieer met swangerskappe wat nie begeer word nie. 'n Sekere en veilige tegniek van hierdie aard moet noodwendig 'n belangrike bydrae lewer tot die vermindering van hierdie soort spanning.

Die prys van so 'n voorbehoedende prosedure speel natuurlik 'n baie belangrike rol in enige besluit of dit toegepas moet word al dan nie. 'n Matige roker wat ongeveer 20 sigarette per dag dwarsdeur die jaar rook, spandeer twee maal soveel as wat sy vrou aan hierdie hormoon as voorbehoedmiddel sal bestee.

Soos die wet op die oomblik lui, verseker die Sesde Bylae in verband met Moontlike Nadelige Medisyne dat noretinodrel outomaties aan die bepalings van die wet onderhewig sal wees, en dat dit dus nie regstreeks aan die publiek oor die apteker se toonbank verkoop sal kan word nie. Dit verseker 'n verdere mate van beskerming en kontrole, want vroue wat hierdie voorbehoedtegniek wil toepas, sal dit ten minste aanvanklik onder die toesig en leiding van 'n mediese praktisyn moet doen, want dit sal onmoontlik vir haar wees om die hormoon sonder 'n dokter se voorskrif te verkry.

Daar is vandag wêreldwye besorgdheid oor die probleem voortspruitende uit bevolkingsbeheer en die beperking van bevolkingstoenames in sekere dele van die wêreld tot 'n peil wat met die ekonomie van die betrokke streek ooreenstem. Dit wil voorkom asof hierdie hormoontegniek 'n besonder doeltreffende manier is om uitvoering op 'n groot skaal aan sulke belangrike beleidsrigtinge te gee, en dat die opleiding van die betrokke vroue in die nodige

The United States Food and Drug Administration has approved the release of norethynodrel as an oral contraceptive, thus indicating their endorsement of this hormone as safe and effective for this purpose.

The Medical Advisory Council of the Family Planning Association, after carefully considering the data on this hormone as a contraceptive measure, has expressed its satisfaction that the hormone is perfectly safe for use in the way planned.[3]

This simple, safe and successful method of contraception should therefore make an enduring and material contribution to the health and happiness of our human society.

tegniek geen groot moeilikhede hoef op te lewer nie.

Die *United States Food and Drugs Administration* het so pas sy goedkeuring geheg aan die beskikbaarstelling van noretinodrel as 'n mondelinge voorbehoedmiddel. Die Departement bekragtig dus dat dit 'n veilige en doeltreffende hormoon vir hierdie doel is.

Die Mediese Adviserende Raad van die *Family Planning Association* het die gegewens oor die gebruik van hierdie hormoon as 'n voorbehoedmiddel sorgvuldig oorweeg, en sy tevredenheid uitgespreek dat die hormoon met volkome veiligheid op die aangeduide manier gebruik kan word.[3]

Hierdie eenvoudige, veilige en geslaagde voorbehoedmetode behoort derhalwe 'n blywende en materiële bydrae tot die geluk en gesondheid van die mensdom te lewer.

ABSTRACTS

ANDROGEN THERAPY IN CASES OF SEVERE LIVER DAMAGE

A method of treatment first described by Girolami, consisting in the administration of large doses of androgen in addition to the standard therapy, was employed in 34 patients suffering from severe chronic liver damage. Twenty-one had cirrhosis and the other 13 chronic hepatitis. Each course of treatment lasted 26 days. During the first 12 days the patients were given 100 mg. testosterone propionate i.m. daily, and during the next two weeks the same dose every other day. Treatment must be continued until permanent compensation is evident or until hepatic function tests yield normal results again. There should be no interval between successive courses of treatment.

The therapeutic results obtained were most satisfactory. Cases of cirrhosis that were still compensated, as well as patients with chronic hepatitis, responded particularly well to androgen therapy. But surprisingly good responses were sometimes also observed in cirrhosis with decompensation. The treatment failed to overcome hepatic coma; in such cases, large intravenous doses of prednisolone are recommended in addition. Among the various androgens, testosterone propionate proved the most suitable. Very large total dosages, amounting to 5,000 mg. in women and as much as 7,000 mg. or more in the case of men, were tolerated without complications.

[Fiegel, G. and Kelling, H. W. (1958): Aerztl. Forschg., **12**, 346].

THE DIAGNOSIS OF ADDISON'S DISEASE

Although Addison's disease is the best known example of adrenocortical insufficiency, its diagnosis can still cause great difficulty to-day since none of its symptoms is pathognomonic. It is also impossible to establish the presence of the disease unequivocally by means of laboratory findings alone.

With the aid of ACTH, however, it is possible, as is explained in an Australian publication, to differentiate between genuine and apparent Addison's disease. Forty units of ACTH are infused in the course of several hours and the urinary 17-OH-corticosteroids are determined; they provide a more sensitive index than urinary 17-ketosteroids. The possibility of Addison's disease can be excluded if 17-OH-corticosteroid excretion rises appreciably after a single infusion; if it does not, an attempt should be made to obtain corroborative evidence by administering ACTH on 3 successive days. On the other hand, determination of the 17-ketosteroids often yields doubtful results, particularly when only a single ACTH infusion has been given. Sodium retention and increased potassium excretion (with a corresponding change in the sodium-potassium ratio) likewise provide corroborative evidence that the patient has responded to ACTH. Observation of the circulating eosinophils, however, has proved less reliable.

ANOXIC CEREBRAL DAMAGE IN BRONCHIAL ASTHMA

A severe complication of bronchial asthma is anoxia which may lead to irreversible cerebral lesions. The literature contains extremely few data on this subject. The author reports on a case in which a state of decortication developed following a severe attack of asthma. The 34-year-old patient was kept alive for almost a year without the neurological picture undergoing any substantial change. During this time, the E.E.G. showed marked alterations which suggested an anoxic cerebral lesion. Histological examination of the brain revealed an area of softening that extended over almost the whole of the cerebral cortex, as well as a cavity approximately the size of a nut in the white matter. Severe softening was likewise found in the corpus striatum and in the globus pallidus. The anoxia had probably also caused damage to the capillary endothelium; this favoured the formation of oedema which, in turn, may have been responsible for the cavity.

The course of the disease was such that the possibility of the anoxia being due to a cause other than the interruption of the oxygen supply during asthmatic attacks could be excluded with a degree of probability bordering on certainty. The E.E.G. is of great importance in the diagnosis and prognosis of severe cases of anoxia.

[Máttyus, A. (1959): Arch. Psychiatr. u. Zschr. Neurol. (G.) **199**, 172].

LONG-ACTING SULPHA DRUGS IN TRACHOMA

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About 1940 it was claimed that the sulpha drugs cured trachoma and it is now accepted by the World Health Organization[1] that the sulpha group as well as the antibiotic group is effective against early trachoma and that these drugs are more effective in combination.

In South Africa good results were obtained[2] by treating African children in schools with antibiotic and other eye ointments, but in each school there was a remainder of uncured cases. One wondered whether they refused treatment, whether their attendance was too irregular for sufficient treatment, whether they were continually re-infected at home, or whether, in fact, they were resistant to treatment.

Reinhards, Weber and Maxwell-Lyons[1] had a similar experience with children in North Africa, but they found that a second course of antibiotic ointment cleared them up. This was not so in South Africa, and the question of adding oral sulphonamide was considered.

The practical difficulties were too great to give 4-hourly treatment, but this problem was solved by the introduction of long-acting sulpha drugs, one of which was used successfully in Australia.[3]

PRELIMINARY CLINICAL TRIAL

A preliminary trial was carried out in a kindergarten school, where 70% of the trachoma cases (diagnosed clinically)* had been cured by ethidium bromide in the form of 0.5% ophthalmic ointment. Boots Pure Drug Co. have this drug in the experimental stage and, although it was effective against trachoma in the laboratory and in this trial, it is too irritating in some eyes for general use as yet.

Nine of the 27 original cases were uncured after 6 months' treatment, so they continued with the eye ointment and 6 were given Midicel (Parke, Davis).

This long-acting sulpha drug contains 0.5 g. sulphamethoxypyridazine per tablet, and half a tablet was taken by these small children daily from Monday to Friday for 2 weeks.

After 3 months, those who took Midicel were all cured (with the exception of one who had been absent from school during treatment), while the other 3 were unchanged.

It was realized that these numbers were too small to be other than an encouragement for larger trials, the results of which are reported in this issue by Hildenbrand.[4]

PLAN OF TREATMENT

It would appear that we have developed a safe, simple and economic way of curing and gradually eliminating trachoma from the African population of South Africa. The Bureau for the Prevention of Blindness is using the following plan for treating 40 schools in an endemic area:

FIRST YEAR

1. In January all scholars are treated twice daily with a suitable eye ointment for 5 consecutive days each month until June.

2. In September only the uncured cases are treated with long-acting sulpha in suspension for 2 weeks. This is done together with eye ointment until December.

SUBSEQUENT YEARS

1. In January all *new* scholars are treated with ointment for 6 months.

2. In September the uncured cases are treated with long-acting sulpha and with ointment.

DISCUSSION

The reasons why sulpha is not recommended for all scholars are (*a*) economic, and (*b*) to reduce the risk of a toxic or allergic reaction to the minimum numbers.

The use of ointment for 6 months is to minimize the risk of re-infection (to which the younger children are liable) as well as to cure the infected cases.

There are two situations which will not be met by this scheme. One is that not all children go to school. The other is that there are not enough ophthalmologists to supervise treatment.

Both objections can be met by the training of African field workers in elementary ocular

* Trachoma virus has been cultured subsequently from similar cases at a neighbouring school.

and general hygiene. They should be appointed to distribute ointment and drugs to schools and to initiate treatment which would be carried out by teachers. Such field workers would also be trained to recognize a normal everted upper lid, and thus be able to pick out those resistant cases requiring sulpha treatment.

Regular supervision would be required.

It is estimated that one such trained field worker would be responsible for a unit of 40 schools, and that he would also provide home treatment for those children who do not go to school.

There is no doubt that such a scheme would eliminate future blindness caused by the ravages of trachoma, and would gradually remove this infectious disease from our midst.

SUMMARY

1. Blanket treatment with eye ointment used 5 days each month for 6 months, followed by individual treatment for un-cured cases, is recommended to eliminate trachoma in an endemic area.

2. Individual treatment consists of a long-acting sulpha drug for 2 weeks with a second course of eye ointment used twice daily for 5 days each month for 3 months.

3. Trained field workers are necessary to assist the work.

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TRACHOMA TREATMENT WITH A LONG-ACTING SULPHONAMIDE (MADRIBON) COMBINED WITH EYE OINTMENT (GANTRISIN)

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It is now generally accepted that many cases of trachoma can be cured by an oral sulphonamide or an antibiotic eye ointment.[1-3] This may be due to the effect on the trachoma virus itself or because this disease burns itself out once the super-infection by other organisms has been cured. A percentage of cases, however, is not cured with eye ointment treatment alone, because a constant high level of the antibacterial substance is not achieved in the tissue with topical application only. A second problem arises in the treatment of Bantu children who cannot be sufficiently well controlled to assure constant use of the substance. Adequate application of an ointment is never guaranteed even if these children are treated by their teachers. It was therefore thought that the results of treatment would be improved if, in addition to the local application, a constant high blood level of sulphonamide could be reached by means of a long-acting single dose 24-hourly. In these circumstances success depends on simplicity of treatment and this was the reason for choosing a long-acting sulphonamide. Sulphadimethoxine (*Madribon,* Roche) appeared to be the most suitable sulphonamide giving a constant therapeutic blood level achieved by a single 24-hourly dose.

The most effective treatment of trachoma could be expected from a combination of systemic treatment with this sulphonamide and local treatment with a 4% ophthalmic ointment of sulphafurazole (*Gantrisin,* Roche). To evaluate this treatment a therapeutic trial was instituted where 3 groups of Bantu school children with trachoma were being treated. Each group consisted of about 50 children.

The first group was treated with Gantrisin eye ointment alone, applied twice daily for 5 days by the teacher at each school. This was repeated after 4 weeks and after 8 weeks. The children were re-examined at the end of each course of treatment.

The second group was treated with Madribon tablets alone, the daily dose being administered by the teacher, viz. 1 tablet (0.5 g.) for 6 days, followed by half a tablet (0.25 g.) for another 12 days, i.e. treatment for 2 weeks with the exception of Sundays. This course was repeated after a 7-week interval with a dose of 1 tablet daily for 6 days. Children up to the age of 7 years received half this dose. All patients were re-examined 4 weeks after the first course and 8 weeks after the second course of treatment.

The third group of children was treated with a combination of Madribon tablets and Gantrisin ointment. The doses were given were identical to those groups 1 and 2.

This therapeutic trial was carried out at 2 schools at Pienaar's River and Hammanskraal.

The schools are in a Native area about 35 miles north east of Pretoria and about 5 miles apart. At Pienaar's River 45 (26%) children suffered from trachoma out of a total of 170 and at Hammanskraal 110 (16%) cases of trachoma were diagnosed in 700 children. The hygiene conditions at both schools were much the same. The trachoma cases at Hammanskraal were divided into 2 groups of 55 each. Since Bantu children seldom attend school regularly, I only succeeded in treating 109 regularly out of the total of 155 trachoma-infected cases. This was the final number re-examined at the end of the trial, 8 weeks after treatment had ceased; 42 children were treated with a combination of tablets and ointment, 35 were treated with tablets alone and 32 with ointment alone. Although actually more children were treated, these are the figures one can count upon for statistical evaluation.

Difficulty arose in the diagnosis of trachoma, firstly, since the area is notoriously dry and dusty and almost all inhabitants show chronic irritation of the conjunctiva, and of these again the majority have at least a few follicles. The definite trachoma cases showed many different grades of inflammation varying from slight redness and congestion of the conjunctiva, to serious inflammation with an infiltration of the entire tarsus.

To make an accurate diagnosis, specifically in the slight cases, all children were examined for the presence of pannus with a slitlamp. The presence of pannus is regarded as a pathognomonic sign of trachoma. It was noticed that some of the earliest cases amongst these school children did not show pannus formation at first. Examination with the naked eye never revealed pannus but once the aid of the slitlamp was enlisted, even the smallest pannus formation could definitely be diagnosed.

With these diagnostic notes in mind, the criteria of division into 3 groups was as follows:

1. Slight cases with a little inflammation and few follicles:

(*a*) *Without pannus.* This group was considered as slight and early trachoma, but for the reasons given the diagnosis must remain a little doubtful.

(*b*) *With pannus.* Here the diagnosis seemed to be more definite.

2. Slight to heavy inflammation of the conjunctiva with the presence of small follicles scattered over the entire conjunctiva, the follicles not covering the conjunctiva completely. There was a variation in the number and size of the follicles:

(*a*) *Without pannus.* This was considered trachoma of medium severity. In the absence of pannus, however, there is still a small degree of doubt about the definitive diagnosis.

(*b*) *With pannus.* Otherwise as in (*a*). In these cases the diagnosis of trachoma was definite.

3. Heavy inflammation with large follicles over the entire conjunctiva and infiltration of the tarsus. In these cases pannus was almost invariably present. The diagnosis here was almost always that of trachoma, even if pannus could not be detected in the early cases.

Note: Scarring is only rarely found, and never in young school children. The few cases seen have not been considered for statistical evaluation.

The same difficulties experienced in setting up diagnostic criteria applied to therapeutic criteria. After 4 to 8 weeks' treatment many

TABLE 1: TREATMENT WITH GANTRISIN EYE OINTMENT

		After 1 Month			*After 2 Months*		
	Number	*Still Active*	*Healed*	*Poor Effect*	*Improved but Still Active*	*Doubtful*	*Clear*
Slight Cases							
Without pannus	2	1	1	1	—	—	1
With pannus	1	1	—	—	1	—	—
Medium Cases							
Without pannus	7	4	3	1	—	2	4
With pannus	17	10	7	3	2	3	9
Severe Cases							
Without pannus	—	—	—	—	—	—	—
With pannus	5	5	—	3	1	1	—
Total							
Without pannus	9	5	4	2	—	2	5
With pannus	23	16	7	6	4	4	9
Grand Total	32	21	11	8	4	6	14

TABLE 2: TREATMENT WITH MADRIBON TABLETS

		After 1 Month			*After 2 Months*		
	Number	*Still Active*	*Healed*	*Poor Effect*	*Improved but Still Active*	*Doubtful*	*Clear*
Slight Cases							
Without pannus	—	—	—	—	—	—	—
With pannus	5	1	4	—	—	—	5
Medium Cases							
Without pannus	8	3	5	2	—	1	5
With pannus	13	8	5	1	—	7	5
Severe Cases							
Without pannus	6	3	3	2	1	—	3
With pannus	3	2	1	—	2	—	1
Total							
Without pannus	21	11	10	1	2	7	11
With pannus	14	6	8	4	1	1	8
Grand Total	35	17	18	5	3	8	19

TABLE 3: TREATMENT WITH GANTRISIN OINTMENT AND MADRIBON TABLETS

		After 1 Month			*After 2 Months*		
	Number	*Still Active*	*Healed*	*Poor Effect*	*Improved but Still Active*	*Doubtful*	*Clear*
Slight Cases							
Without pannus	4	2	2	—	—	1	3
With pannus	1	—	1	—	—	1	—
Medium Cases							
Without pannus	14	5	9	—	—	2	12
With pannus	9	1	8	—	1	1	7
Severe Cases							
Without pannus	—	—	—	—	—	—	—
With pannus	14	10	4	—	1	4	9
Total							
Without pannus	18	7	11	—	—	3	15
With pannus	24	11	13	—	2	6	16
Grand Total	42	18	24	—	2	9	31

cases showed no signs of either active trachoma or trachoma at all; yet there was usually slight irritation or even inflammation of the conjunctiva and the presence of some follicles. Since in the dry, windy and dusty areas irritant conjunctivitis is always present, it had to be determined whether the residual inflammation was due to chronic irritation or was trachomatous. The following therapeutic criteria were therefore adopted:

1. *Poor effect.* Only the super-infection appeared to be better but improvement was not marked.

2. *More marked improvement,* but still active trachoma present.

3. *Healing,* but to a doubtful degree.

These are the most difficult cases to assess since one cannot separate trachomatous (super-infection) conjunctivitis from the heat and dust group of the irritant condition.

In this group no sign of active trachoma could be detected after treatment.

4. *Condition completely cleared up,* with no sign of either trachoma or inflammation.

The therapeutic response is summarized in the Tables 1–3.

CONCLUSION

From the results obtained there is no doubt that the best therapeutic response was achieved by the combined treatment with topical ointment and the long-acting oral sulphonamide.

Of the 42 cases treated, 31 cleared up completely (the most marked therapeutic response, i.e. clear, which is interpreted as healed).

All cases showed a definite improvement and only 2 were still active at the final examination; 9 cases showed slight inflammation of the conjunctiva after 8 weeks' treatment but no sign of active trachoma. Those 9 cases were designated as 'doubtful but probably healed.'

Statistically, this means that of 42 cases only 2 were definitely unresponsive (5% resistant cases); 73% were definitely healed but this figure could probably be increased to 95% if a further follow-up could have been done.

Compared to this, the results of treatment with Madribon tablets alone were as follows:

Of the total of 35 cases treated, 19 (55%) showed complete response. If to this figure were added another 8 cases which were probably healed the response would represent 84%. Three cases improved but were definitely still active at the final examination; 5 cases showed some response but not sufficient to be called 'healing.' If the 3 improving cases and the 5 failures are grouped together as 'no response,' the failure rate is 16%.

Compared again with the above figures the therapeutic response to treatment with the eye ointment alone was as follows:

Of the 32 cases treated, 14 appeared clear, representing 44%. Twenty cases were healing but doubtful, i.e. 62%. Still active, 12 cases of which 8 showed practically no improvement. Unresponsive therefore, 38%.

The number of seriously infected cases with pannus is small, but the results show a striking difference in favour of treatment with tablets and ointment together. It is significant that 9 of the 14 serious cases heavily infected with trachoma cleared up completely, 4 showed healing, but the end result at the time of writing is still doubtful; only one did not respond at all and showed active trachoma. All cases improved under treatment, even those which for statistical purposes have been termed 'resistant' or 'unresponsive'. Six of the particularly severe cases were treated with Madribon tablets alone. Of these, 3 cleared up completely, 3 showed active trachoma, of which 2 appeared to show no improvement.

Finally, 5 heavily infected cases treated with ointment alone presented only one with doubtful healing, one improved but still active, and 3 with no effect.

It may be that longer and more intensive treatment with ointment alone could give somewhat better results, but, from previous therapeutic experience, the dose given in this therapeutic trial was considered sufficient for optimal results.

The South African National Council for the Blind is at present studying the entire question of treatment of trachoma with a variety of eye ointments in 40 schools in the Northern Transvaal. It will be interesting to compare these results in due course with those of the therapeutic trial reported here.

SUMMARY

An initial population of about 150 school children with trachoma in different stages of infection was divided into 3 groups for treatment. One group was treated with a sulphonamide eye ointment only (Gantrisin, Roche 4%); a second group was treated with a long-acting sulphonamide oral preparation (Madribon, Roche); and a third group was given combined treatment with the sulphonamide ointment and the long-acting sulphonamide tablets.

The percentage of healing and healed cases left no doubt that the combined treatment (topical and parenteral) showed the greatest therapeutic response. In this combined group, the percentage of healed cases was at least 73% but might probably have been as high as 95%. There were fewer resistant cases after the combined treatment (5%) than with either Gantrisin alone (38%) or Madribon alone (16%).

My sincere thanks go to the Secretary and staff of the South African National Council for the Blind for their cooperation and encouragement; to Roche Products who provided the complete supply of Gantrisin ointment and Madribon tablets; and to Dr. W. Leigh of Roche Products (Scientific Department) for his help in planning the therapeutic trial, his valuable assistance in connexion with the dosage schemes and for the literature supplied.

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STEROID TREATMENT OF BRONCHOSPASM

A PRELIMINARY REPORT ON PREDNISONE, PREDNISOLONE AND METHYL PREDNISOLONE

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After 12 years of study with cases of bronchospasm, the author has developed a strong conviction that steroids should play a greater part in the treatment of this distressing symptom. The drug should be used very early in the disease and also in cases of moderate severity, as the symptomatic response is dramatic, and of great reassurance to the parents, who then realize that this condition is not necessarily chronic or disabling.

The approach to the problem in this series has been purely clinical in an endeavour to obtain benefit with low doses of steroids and the minimal amount of investigation.

The series is too small for a statistical comparison between the 3 steroids. More extensive research is highly desirable to determine the relative roles of infection, allergy and psychological disturbances in the aetiology of this symptom. To obtain a balanced and unbiased view, a team should be formed, consisting of a paediatrician, a psychiatrist and an allergist, with laboratory facilities.

The word *bronchospasm* has been chosen deliberately as parents have a dread of the word *asthma*. This word should be removed from the vocabulary of paediatricians. The terms are interchangeable and may be defined as recurrent attacks of bronchial spasm, associated with wheeziness and difficulty in breathing. The underlying pathology appears to be partial obstruction of the bronchial tree due to increased bronchiolar secretions and oedema of the mucous membrane, associated with spasm of the bronchiolar muscles. As the condition progresses, a chronic condition develops in which the mucous membrane is permanently thickened and associated with hypertrophy of the bronchiolar musculature. This results in emphysema and a tendency to develop a low-grade infection. The difference in the results between children and adults is therefore not comparable, as not only are the pathological changes often not reversible, but an adult also develops patterns of behaviour which, to a large extent, become fixed and more difficult to control.

In nearly every case in the present series, which has ben followed since February 1959, the onset has been before the age of 3 years; and in every case the history starts with recurrent infection of the chest, which later recurs with increased severity and frequency, accompanied by wheeziness. This history has been striking in nearly all cases under the author's care in the last 10 years. A history of bronchospasm in the family has been present in a number of cases and in a few also a history of eczema. Any interpretation of the value of therapy should be treated with great scepticism and caution, as attacks are inclined to subside spontaneously, and also to disappear between the ages of 5 and 10 years without treatment. Nearly every form of therapy reports benefit in at least 50% of cases. This is really a poor result, as spontaneous cure occurs in at least 80% of cases.

When the author first started treating cases of bronchospasm, the great part played by infection appeared to be paramount. Cases were treated therapeutically and prophylactically with penicillin and sulphonamides and the temporary results were good, but after 3–4 months these antimicrobial agents seem to lose their potency, and nearly all cases relapsed.

Later, the author treated a great many cases with prophylactic Aureomycin in a daily dose of 100 mg. and he was greatly impressed with the results. Unfortunately, after 6 months many cases relapsed. He then used Aureomycin in short intensive courses and the results were reasonably good.

Then 3 cases were seen which changed the whole programme of therapy. These cases are briefly as follows:

Case 1. Linda, a girl of 12 years who had had bronchospasm in England since the age of 1 year, had come to this country at the age of 7 years. The attacks persisted almost daily. She was treated with prednisone and within 24 hours she was perfectly well and has remained so far the past 5 years.

Case 2. Yvonne, 7 years old, gave a 5-year history of bronchospasm. The mother was about to go to a psychiatrist because she was

completely distraught about the child's chest.

This child was treated with prednisone and within 2 or 3 months was also perfectly well and has remained so to date.

Case 3. This boy developed recurrent attacks of bronchospasm, preceded by a cold or sore throat. He was ill off and on for 2 years and responded reasonably well to short symptomatic treatment with prednisone, but relapsed soon after treatment ceased. His tonsils appeared to be unhealthy, so they were removed. He had one further attack (which responded to the regime outlined below) and has remained well since.

When the author first treated cases of bronchospasm only the severe chronic cases were treated with steroids. As the results were so good, any case with a history of bronchospasm was then put on a full course of treatment and the results have been even better.

The children were treated alternately with prednisone (5 mg.), prednisolone (5 mg.) and methyl prednisolone (Medrol, 4 mg.). They were given 1 tablet 3 times a day for 3 days; then 1 tablet twice daily for 4 days; and then 1 tablet nightly for 2–3 weeks; later ½ tablet at night for a further 3 weeks. If the attacks relapsed, the dosage was increased temporarily.

The children were also put on to Amodrine ½ tablet *t.d.s.* while the spasm lasted. For the cough they were given Syr. Codein. Phosph. 1 dram *b.d.* or *t.d.s.* for any child over the age of 3 years. No side effects were reported. This cough mixture has been used for 10 years in this dosage without ill effect. Another good cough mixture is equal parts of Syr. Codein. Phosph., Syrup Cocillana Co. and Benadryl Syrup. In the past year Orthoxine tablets have been used in place of Amodrine with equally good results. A most interesting point has been that throughout the course of therapy, no antimicrobial cover was given, although this is frowned upon by most authorities. No antimicrobial agent was necessary because, in the dose of steroid used, the suppressive effect on the adrenals does not take place.

COMMENT ON PREDNISONE

In the 14 cases in this group the results have been very good in 13 cases. In Case 12 the results with combined prednisone, prednisolone, coryzal vaccine and tonsillectomy were not satisfactory. In this case, however, there is much doubt whether the mother was cooperative. This mother brought the child at the age of 3 years, when she was given prednisone with good effect and then did not return again until the child was 8 years old. In 3 other cases the good results were only obtained after a mixed coryzal vaccine prepared by the S.A.I.M.R. had been given in addition. In no case were any side effects noted.

COMMENT ON PREDNISOLONE

In this group there were 8 cases. Six of these cases did very well. In 2 cases there was a definite improvement, but the condition is still present. In one case the patient did very well, but the child developed slight evidence of a moon face and gained 5 lb. in weight.

COMMENT ON METHYL PREDNISOLONE (MEDROL)

In this group there were 11 cases. Of these 9 did very well. Included are 2 cases which appear to have done better on Medrol than on prednisone. In one case the child was definitely much better but is still having slight attacks periodically. In another case the result was a definite improvement, according to the mother, but in the opinion of the author it is not entirely satisfactory. The child has been treated with prednisone, Medrol, also Depot Medrol (Medrol by injection, when it is supposed to have a slow rate of absorption) and coryzal vaccine (Appendix 1).

DISCUSSION

In attempting to compare the 3 steroids used in this experiment, it would only be fair to state at the outset that the number in the series is small, and that the follow-up is inadequate. With this in mind, it must be remembered, however, that all these cases were seriously ill patients with a chronic illness, who had all done badly with previous therapy. The steroids have undoubtedly helped many and, in the opinion of the parents, all have been improved. It may also be dogmatically stated that if steroids are used intensively in an acute episode of bronchospasm, then only the exceptional case would have to be hospitalized.

Except for one case in the 3 groups, no case developed any side effects with the dosage used. This would seem to indicate that larger doses which are frequently recommended do not appear to be necessary for good therapeutic effect except for an acutely ill child during an acute episode.

A word about the failure to give antimicrobial therapy while on steroids. This has been commented on earlier by the author, but he would be prepared to retract if it is shown to be a dangerous omission.

CASE REPORTS

TABLE 1: RESULTS OF STEROID TREATMENT

Case No.	*Identity*	*Age (Years)*	*Duration of Illness (Years)*	*Result*
			PREDNISONE	
1	P.B.	3	2½	This child has done very well.
2	S.P.	6	1	This child has done well on prednisone + coryzal vaccine.
3	C.K.	2½	2	Undoubtedly not helped by prednisone alone, but with vaccine has had wonderful result.
4	L.B.	3	¼	This patient has done very well.
5	M.H.	7/12	½	Has done very well on prednisone + coryzal vaccine.
6	K.S.	13	10	Has done very well.
7	H.V.D.W.	2½	1½	Result very good.
8	S.R.	4½	2	Good.
9	M.J.	2½	5/12	This child has done very well.
10	J.M.	9	2	This child has done very well.
11	K.D.R.	2	2/12	This child has done very well.
12	C.B.	8	7	This child has not done well on prednisone, prednisolone or coryzal vaccine separately or together.
13	L.S.	2½	2	To date the child has done very well.
14	J.S.	12	8	Too early to assess, but is reasonably well controlled.
			PREDNISOLONE	
15	A.K.	5	3	This child has shown a marked improvement and only has an occasional relapse.
16	H.J.	4	1½	Good result.
17	W.F.	1½	1¼	Good result so far.
18	D.T.	2½	2	This patient has done reasonably well.
19	G.G.	3½	½	Much improved.
20	R.U.N.	3	½	Very good result.
21	S.R.	4	3	In view of the severe history the result can be considered reasonable but not wholly satisfactory.
22	G.H.	5½	4½	This child has shown a very good result except for slight evidence of moon face, which was very mild.
			MEDROL	
23	A.B.	3½	¼	Definitely greatly improved.
24	A.H.	5	4½	Has done well to date.
25	C.A.	7	4	Has done well to date.
26	C.B.	1½	¾	Much improved.
27	C.A.B.	3	¼	Has done exceptionally well.
28	J.M.	11½	11/12	Has done exceptionally well.
29	P.H.	3½	1½	Appears to have done better on Medrol than on prednisone. The first drug may have been given inadequately.
30	T.S.	7	⅓	This child's attacks are controlled, but he still has slight attacks periodically.
31	T.F.	6	½	This child apparently did better on Medrol than on either prednisone or Deronil. Prednisone apparently made him excitable.
32	B.S.	3½	1½	This child, according to the mother, is much better There was no difference between prednisone and Medrol. Vaccine did not help. Depot-Medrol in 2 c.c. dose only lasted a week: not as good as oral Medrol.
33	T.W.	2½	1½	This child has been helped a great deal and seems to have done well.

The difference between prednisone, prednisolone and methyl prednisolone is slight although in 3 cases on prednisone the results would not have been good without the coryzal vaccine. In the case of prednisolone, however, 2 cases did reasonably well, although the result cannot be considered good. In the case of methyl prednisolone 9 cases have done well and 1 reasonably well; included are 2 who did not do well on prednisone. In one case, however, the result was poor with all 3 types of steroids plus tonsillectomy and coryzal vaccine.

The role of allergy in bronchospasm is undoubtedly of some importance, but a number of points are puzzling. If a child is carefully followed it will be noted that the onset of bronchospasm is usually preceded by a coryza or upper respiratory infection which slowly increases in severity. Later, bronchospasm of increasing severity develops. If the bronchospasm is due to an allergic cause, such as pollens, dust, food and bacterial products, the onset should be sudden in all instances; perhaps not in the first attack, but certainly in every following attack. An individual who is sensitive to a drug or pollen usually shows an immediate reaction when exposed to the responsible agent. If allergy is so important in this condition, why does the individual remain well for a long time or even permanently after a full course of steroids? If the steroids interfere with the antigen-antibody response, then there seems to be a definite place for their use in place of specific desensitization. It is often found that the skin test reaction bears no relationship to bronchospasm as determined by the history of the case.

The problem of tonsillectomy is an interesting one. Frequently it is recommended that on no account should they be removed as the patient is a so-called 'allergic subject'; yet it is often found that an essentially healthy individual with no history of chest complaints or allergy may have the tonsils removed and later develop attacks of bronchospasm. Just as often a child with bronchospasm may have a tonsillectomy and afterwards be free of chest symptoms. The author therefore recommends that if there are sufficient grounds for tonsillectomy *per se*, i.e. frequent attacks of tonsillitis, the tonsils should be removed. This often results in marked improvement, not only in the bronchospasm, but also in the general well-being of the individual.

The hypothesis which is postulated is as follows:

At an early age the infant starts with whooping cough or upper respiratory infection. This results in bronchospasm which recurs with increasing severity with subsequent infections. The child then develops a tendency to bronchospasm with every infection and develops a so-called 'tendency' to bronchospasm. This 'tendency,' if not stopped, subsequently leads to bronchospasm through many other stimuli, such as dust, inclement weather, pollens and even psychological factors. The agents cause increased stimulation of bronchiolar secretion and consequent bronchiolar spasm. If controlled early, the so-called 'conditioned pattern of response' would not develop. In adults the results are not as good, because the changes have become permanent.

SUMMARY

In a series of 33 cases the value of steroids in bronchospasm has been shown to be highly efficacious. The comparative value of prednisone, prednisolone and methyl prednisolone requires further investigation.

The failure to administer antimicrobial therapy during treatment has been deliberate and has not caused any anxiety.

The role of allergy in the causation of bronchospasm needs further evaluation as the results with steroids are long-lasting and often permanent.

The side effects in this series have been minimal, as also in some 200 other cases treated on the same regime by the author. The dosages used have been substantially the same in all cases, and appear to have been adequate.

Two additional aids to treatment which have been of value are the use of mixed coryzal vaccine and tonsillectomy when specifically indicated.

The follow-up has been too short.

Special thanks to the Upjohn Company, which made large supplies of Deltasone (prednisone), Deltacortef (prednisolone) and Medrol (methyl prednisolone) freely available, with special mention of Mr. D. Moffson, whose encouragement and enthusiasm have stimulated this report.

APPENDIX 1

	Organisms per c.c. (in millions)
Mixed Coryzal Vaccine Number 3	
Pneumococcus (various strains)	300
Staphylococcus	300
Bacillus of Friedländer	300
Streptococcus	300
H. Influenzae	150
M. Catarrhalis	150
Total	1,500

DISORDERS OF THE GASTRO-INTESTINAL TRACT

STELABID IN THEIR TREATMENT

S. S. ROWELL, M.B., B.S., M.R.C.S., L.R.C.P.
and
L. P. SAYERS, B.A., M.B., B.CH., B.A.O.
London

Stelabid is a combination in a single tablet of 5 mg. isopropamide iodide (Tyrimide) and 1 mg. trifluoperazine (stelazine).

Isopropamide iodide is one of the more recent synthetic anticholinergic agents which has already been used successfully in the treatment of gastro-intestinal complaints, presumably because of its action in reducing gastro-intestinal motility and secretion.[3, 12, 15] However, it is common experience that anticholinergic drugs by themselves give disappointing results in long-term management of these cases.[9, 11, 14] This may be due to the fact that the concomitant predisposing central nervous and emotional factors are still present. The need for controlling these neurogenic components has been long recognized and barbiturates have been regularly prescribed as part of the treatment.

Because of this, it was decided to augment the effect of isopropamide iodide with one of the newer tranquillizers, trifluoperazine. This drug is established in the treatment of a wide variety of psychoneurotic conditions.[2, 4, 6, 10] Amongst these are anxiety, tenseness and hyperactivity which are commonly associated with disturbed gastro-intestinal function and thought by some to have an aetiological significance. A possible added advantage of trifluoperazine is that it has a specific anti-emetic effect and has been used successfully in suppressing nausea and vomiting associated with conditions such as pregnancy, gastrectomy and gastro-enteritis.[5, 6, 10, 13]

It was decided, therefore, to carry out a trial of this combined drug in a series of patients presenting themselves in general practice with a variety of gastro-intestinal disturbances in which abdominal pain and nausea and vomiting were the predominant symptoms.

MATERIAL AND METHODS

The patients were selected mainly on the basis of the chronicity of their condition and the failure to respond to the more usual treatment of various combinations of diet, alkalis, belladonna and phenobarbitone.

Fifty-two patients started treatment with Stelabid. Of these, 15 failed to complete the course, either because they did not return after the first consultation or because they refused to continue taking the tablets.

Included in the remaining 37 patients were 13 cases diagnosed as chronic peptic ulcer, 10 as chronic gastritis and 6 as acute oesophagitis, gastritis or duodenitis. Twelve of the patients with suspected peptic ulcer were examined radiologically and in 11 the diagnosis was confirmed.

As an arbitrary division, it was decided to class all those who had signs and symptoms persisting for more than 3 months as chronic and for less than one month as acute. Of the 31 in the chronic groups, 24 had suffered from the same condition for over a year and 15 for over 3 years.

The treated group included 22 men and 15 women in the age range 22–69 years.

Each patient was treated for 4 weeks with 1 tablet of Stelabid twice a day. A weekly analysis of signs and symptoms was recorded and an overall assessment made at the end of the treatment period.

A response was considered satisfactory if there was a complete remission of symptoms, such as pain, nausea and vomiting and a disappearance of objective signs, such as abdominal tenderness, within 4 weeks. All other cases in which there was no improvement or if improvement was not complete, were graded as unsatisfactory.

RESULTS

The results of treatment are summarized in Table 1. Thirty-two of the 37 patients who completed the course of treatment had a satisfactory result and, in the majority of cases, the improvement was marked, if not complete, within the first 2 weeks. In only 7 in this group was the full 4 weeks necessary for a complete recovery. One of the most dramatic results was seen in a patient who had suffered from a gastric ulcer and for whom surgery was considered essential, but was refused.

Ten of the patients in this series had a marked psychogenic component with initially such symptoms as anxiety, tenseness and hyperexcitability; 8 of these became more relaxed after one or two weeks of treatment. Two showed no improvement physically or mentally.

The drug was very well tolerated and the only side effect complained of was nausea after taking the tablet in one case and constipation in another.

ber of cases, the tranquillizing effect certainly played a part in improving the condition.

Similar results have been recorded by Arden[1] and Platt.[7]

SUMMARY

1. Stelabid, a combination of isopropamide iodide (Tyrimide) and trifluoperazine (Stelazine) has been used for the treatment of 37 cases of gastro-intestinal disorder.

TABLE 1: THE RESULTS OF STELABID TREATMENT

Diagnosis		*Result*		*Duration of Symptoms*
		Satisfactory	*Unsatisfactory*	
Peptic Ulcer	Chronic Gastric	1	—	3 months—
	Chronic Duodenal	8	—	25 years
	Unspecified	2	2	(average 7.4 years).
Chronic Gastritis		10	1	3 months—6 years (average 2.0 years).
Acute Oesophagitis, Gastritis and Duodenitis		6	—	
Other Gastric Conditions		4*	1†	
Colitis		1	1	5—6 years.
Totals		32	5	

*2 cases vomiting following gastrectomy, 1 vomiting of pregnancy and 1 gastritis associated with achlorhydria
†1 case vomiting following gastrectomy.

DISCUSSION

Since the types of gastro-intestinal conditions found in this series are examples of those which will frequently improve without treatment and respond satisfactorily to simple procedures, such as attention to diet and administration of alkalis, it is difficult to evaluate the relative effectiveness of this drug.

However, the results indicate that Stelabid is a valuable form of treatment for a variety of gastro-intestinal disorders and there is the impression that it is better than the more usual forms as, in the majority of cases in this trial, these had previously failed to control the condition. It is interesting to note that in 4 of the successful cases, previous treatment with an anticholinergic agent alone had failed. In two of these the agent was isopropamide iodide and in two probantheline bromide. In a number of cases, the tranquillizing effect certainly played a part in improving the condition.

2. The response to treatment was marked in the majority of cases within 2 weeks and complete in 32 cases within the month; 11 of the 13 cases of chronic peptic ulcer, 10 of the 11 cases of chronic gastritis and all 6 cases of acute gastro-intestinal upset responded satisfactorily.

3. The comparison with previous therapy and the subjective response of a number of the patients indicate the value of the addition of a tranquillizer to a therapeutic regime.

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NOTES AND NEWS : BERIGTE

Dr. Bernard Levinson, M.B., B.Ch., D.P.M. (Rand), has commenced practice as a Psychiatrist at 504 Osler Chambers, Jeppe Street, Johannesburg. (*Telephones*: —*Rooms*: 23-9860; *Residence*: 42-9686).

* * *

Mr. Ian H. Leitch, F.R.C.S. (Eng.), has commenced practice as an orthopaedic surgeon in partnership with Mr. D. J. Retief at 203 Osler Chambers, 215 Jeppe Street, Johannesburg. (*Telephones*: *Rooms*: 23-7988/9; *Residence*: 48-8717).

* * *

Prof. Allan Kark, formerly Head of the Department of Surgery, University of Natal, Durban, has left for New York to assume an appointment as Director of Surgery and Surgeon-in-Chief, Mount Sinai Hospital, New York.

* * *

Dr. Lance Human, M.B., Ch.B. (Pret.), F.R.C.S. (Ed.), has commenced practice as a specialist surgeon at Medical Centre, 110 Park Drive, Port Elizabeth. (*Telephones*: *Rooms*: 3-3733; *Residence*: 51-2968).

* * *

Dr. David Glajchen, M.B., B.Ch. (Rand), M.R.C.P. (Edin.), has commenced practice as a specialist physician at 704 Medical Centre, Jeppe Street, Johannesburg. (*Telephones*: — *Rooms*: 22-9440; *Emergency*: 22-4191).

* * *

Dr. Oscar M. Rosenzweig, M.B., B.Ch., D.A. (Rand) has commenced Anaesthetic Practice in partnership with Drs. S. I. Weinstein and S. P. Josman at 305 Osler Chambers, Jeppe Street, Johannesburg. (*Telephones*— *Rooms*: 23-0955; 22-2142; 23-8727; *Residence*: 42-3059).

* * *

TWO NEW CHAIRS AT THE DURBAN MEDICAL SCHOOL

The Council of the University of Natal recently conferred Professorships on Dr. H. L. Wallace and Dr. H. Grant-Whyte of Durban.

Professor Wallace is the Head of the Sub-Department of Paediatrics of the University of Natal at the King Edward VIII Hospital, and is also Senior Physician at the Addington Children's Hospital, Durban.

Professor Grant-Whyte is Head of the Sub-Department of Anaesthetics of the University of Natal at the King Edward VIII Hospital, and is also Head of the Department of Anaesthesia at Addington Hospital.

PREPARATIONS AND APPLIANCES

DORMWELL

A SAFE, NON-BARBITURATE HYPNOTIC

Evans Medical announces the introduction of **Dormwell** Tablets and **Dormwell** Paediatric Tablets, manufactured by Smith & Nephew (Pharmaceuticals) Ltd., Welwyn Garden City, Herts, England.

Dormwell is dichloralphenazone, a molecular complex of chloral hydrate and phenazone. It is a safe, non-barbiturate sedative and hypnotic.

Dormwell Tablets, available in containers of 25 and 250 tablets; each contains 10 grains of dichloralphenazone. **Dormwell** Paediatric Tablets each contains 2½ grains.

As a hypnotic, dichloralphenazone induces drowsiness in 15 minutes and quiet, deep sleep within the hour, lasting for 5–8 hours. All the hypnotic and sedative properties of chloral hydrate are retained without the penetrating, unpleasant odour and the danger of gastric irritation. In addition, **Dormwell** possesses mild, analgesic properties which are an advantage in the management of insomnia associated with slight pain.

It is particularly suitable for elderly patients as it causes no restlessness or mental confusion. It is very well tolerated by children and babies.

Dosage and Administration: **Dormwell** Tablets should be swallowed whole with a good draught of water.

Hypnotic: 2 tablets 20 minutes before retiring. Patients with a history of long and heavy sedation may need larger commencing doses.

Sedative: ½ to 2 tablets.

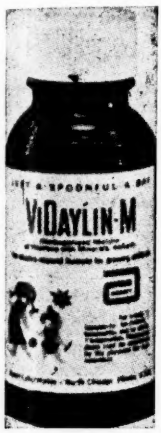
Dormwell *Paediatric Tablets: Hypnotic.* 1–3 *Years*, 1–2 tablets (maximum 4 tablets); 3–6 *Years*, 2–3 tablets (maximum 6 tablets).

Sedative: Half the average hypnotic dose.

Literature and samples may be obtained from Evans Medical, P.O. Box 6607, Johannesburg.

VI-DAYLIN-M

Abbott Laboratories announce the introduction of a new addition to their well-known Vi-Daylin range.



The new preparation is called **Vi-Daylin-M,** and contains 9 important vitamins, 8 valuable minerals, plus lipotropic factors.

Vi-Daylin-M is a citrus-flavoured nutritional supplement. In syrup form, it appeals particularly to children. However, it is also enjoyed by older patients who for one reason or another cannot tolerate tablets and would prefer a liquid nutritional preparation.

Indications: **Vi-Daylin-M** is highly effective as a dietary supplement for the prevention and the treatment of vitamin-mineral deficiencies. It is of particular service in cases of improper diet, poor intestinal absorption, and whenever an increased amount of vitamins and minerals are desired.

Daily Dose: For *infants*, ½ teaspoonful; for *children*, 1 teaspoonful, and for *adults*, 2 teaspoonfuls.

Therapeutic doses should be determined by the physician for each individual.

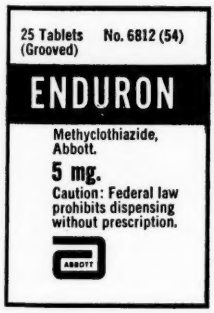
Vi-Daylin-M is packed in a 4-oz. bottle and enclosed in an elegant plastic container.

The price to the public is 95 cents (9s. 6d.)

ENDURON

A new and valuable one-a-day diuretic, **Enduron,** marketed by Abbott Laboratories is now available in South Africa.

Enduron (methyclothiazide, Abbott) is claimed to be the logical culmination to thiazide therapy. The predominant effects of **Enduron,** are diuresis, natruresis, and chloruresis. Serum potassium levels are little affected. Although the excretion of sodium is greatly enhanced, the excretion of potassium is not increased proportionally. Consequently, potassium depletion infrequently presents a problem in patients treated with **Enduron.**



Clinically **Enduron** offers several important advantages when compared with the older benzothiadiazines:

1. **Enduron** leads to greater sodium excretion per unit of potassium excreted and to less total potassium loss than other benzothiadiazines.

2. **Enduron** has a duration of effect of at least 24 hours—longer than other benzothiadiazines—affording satisfactory therapy with one dose daily.

3. **Enduron** is highly potent; 10 mg. produces as great a natruresis as the peak effect of any available benzothiadiazine.

For the maintenance of an oedema-free state or as an adjunct in the management of hypertension, 2.5 to 5 mg. of **Enduron** once daily usually will be sufficient.

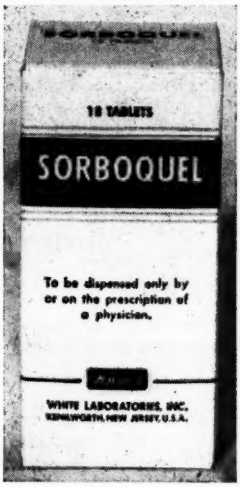
Enduron is packed as 5 mg. grooved tablets in bottles of 25.

SORBOQUEL

WHITE LABORATORIES INC., KENILWORTH. U.S.A. FOR THE SYMPTOMATIC CONTROL OF THE DUAL PROBLEM OF ACUTE AND CHRONIC DIARRHOEA: TOO FLUID FAECES, TOO RAPID EVACUATIONS

Description: Each tablet contains 0.5 g. polycarbophil and 15 mg. thihexinol methylbromide.

Indications: **Sorboquel** Tablets are indicated for the dual problem of acute and chronic diarrhoea: too fluid faeces, too frequent evacuations. **Sorboquel** is also indicated in the treatment of irritable bowel syndrome, regional enteritis, diverticulitis and ulcerative colitis, postantibiotic enteritis, malabsorption syndrome, radiation proctitis, surgically short-circuited intestinal states.



Advantages: Polycarbophil is an inert synthesized macromolecular substance with an extraordinary water-binding capacity and is not absorbed from the intestine. Its marked absorption of free faecal water, characterizing diarrhoeal states, produces formed stools of normal consistency. The exceptional hydrosorptive action of polycarbophil is initiated only on reaching the slightly acid or alkaline medium of the small intestine or colon.

Dosage: Adults and Older Children:—Initially 2 **Sorboquel** Tablets followed by one *q.i.d.* are usually adequate. Depending on the severity of diarrhoea, divided daily dosage of 6 or even 8 tablets may be required initially in some cases. Doses exceeding 6 tablets a day should not be employed over prolonged periods. Maintenance dosage, 1 to 3 tablets daily.

Scherag (Pty.) Limited, P.O. Box 7539, Johannesburg.

PARSTELIN TABLETS

Each **Parstelin** tablet contains 10 mg. **Parnate** and 1 mg. **Stelazine.**

Indications:

1. Symptoms of depression and anxiety appearing concurrently.
2. Emotional fatigue.
3. Menopausal syndrome.
4. Emotional states, secondary to organic illness, and psychosomatic illnesses with symptoms of depression and anxiety.

Parstelin enables the physician to control *with a single preparation* the symptoms of depression and anxiety when they appear concurrently. The need for such a product has long been realized. The association

of **Parnate,** a new antidepressant agent that is particularly effective in mild and moderate depressions, with **Stelazine,** a phenothiazine tranquillizer outstandingly effective in treating anxiety, is a logical development in this field.

Dosage: Usual dosage is 1 tablet twice a day (morning and afternoon).

Presentation: Tablets, in containers of 25 and 250.

Further information may be obtained from SKF Laboratories (Pty.) Ltd., P.O. Box 38, Isando.

PARNATE TABLETS

Each **Parnate** tablet contains 10 mg. of trans-dl-2-phenylcyclopropylamine as the sulphate.

Indications: Pure depression (reactive endogenous); involutional melancholia, manic-depression psychosis (depressive phase), psychotic depressive reactions.

Pharmacologically, **Parnate** is a monoamine oxidase inhibitor with marked antidepressant properties. It is indicated in all types of depression, and has a considerably faster action than previous antidepressant agents; as it is not a hydrazine derivative it is free from toxicity potential of the MAO inhibitors related to hydrazine. Maximum therapeutic benefit is often obtained within 7 days; there are no serious side effects, and the action of the drug persists for only 48–72 hours after withdrawal.

Dosage: 10 mg. twice daily (morning and afternoon).

Presentation: Tablets, in containers of 25 and 250.

Further information may be obtained from SKF Laboratories (Pty.) Ltd., P.O. Box 38, Isando.

TRESCATYL

Maybaker (S.A.) (Pty.) Ltd. announce that **Trescatyl** brand ethionamide is available in containers of 50 x 250 mg. tablets, in addition to the pack of 250 x 250 mg. tablets.

It is thought the smaller package will be more convenient for the filling of prescriptions relating to patients discharged from tuberculosis institutions, but who still require drug cover.

INTRAVAL SODIUM

Maybaker (S.A.) (Pty.) Ltd. announce a change in the packing of **Intraval** sodium in that the pack of 6 x 0.5 g. ampoules with 6 x 10 ml. ampoules water for injection (for the preparation of the 5% solution) has been replaced by a pack of 5 x 0.5 g. ampoules with 5 x 10 ml. water for injection.

REVIEWS OF BOOKS

SURGERY OF THE RETINA

Importance of the Vitreous Body in Retina Surgery with Special Emphasis on Reoperations. Ed. by Dr. Charles L. Schepens. (1960. Pp. 226 + Index. With 133 Figs. £6 7s. 6d. (R12.75)).
St. Louis: The C. V. Mosby Company.

Although the eye is a small organ, the human vitreous is the largest mass of intercellular connective tissue in the body. It is situated at the very centre of the visual organ. In spite of its size and situation it has been, in the past, rather neglected. Recent interest in the vitreous by clinical ophthalmologists stems from the observation that implants of vitreous material are of value in some cases of detached retina and from the demonstration of a relationship between abnormalities in the vitreous structure and the formation of retinal holes.

This volume is a record of the Second Conference of the Retina Foundation. The participants are distinguished American and European doctors and their papers contain a great deal of very useful information upon the vitreous and indeed, on detachments of the retina in general, which is not easily available elsewhere.

New diagnostic methods have become available for the study of the posterior segment of the eye since World War II. They include the Hruby lens, the Goldman 3-mirror contact lens and the 4-mirror gonio-prism of Allen-Thorpe. The new instruments require new skills for their use and the observations made with them have to be interpreted and understood. There is not yet full agreement on the meaning and significance of all the observations made. This will take time to work out.

This volume contains valuable chapters on the anatomical relationships of the retina to the vitreous body, on the physiology of the vitreous body and on pathologic findings after retinal surgery. Hruby writes on clinical observations of vitreous change and Schepens on ophthalmoscopic observations related to the vitreous body. Shafer describes the technique of vitreous implantation. Pischel writes on scleral resections and Okamura on scleral buckling procedures.

Not the least interesting part of the book is the discussion of papers by other members of the forum.

Weve has expressed the view that the next generation of ophthalmologists will be able to cure all detached retinas. The work described in this excellent symposium lends support to this optimistic view. The book is heartily recommended to all who are interested in the treatment of retinal detachments.

HANDBOOK FOR ZULU PATIENTS

Handbook to Aid in the Treatment of Zulu Patients. By G. D. Campbell and Harry C. Lugg. (1960. Pp. 131 + Loose Index).
Natal: Natal University Press.

Medical practitioners and nurses working both in the cities and further afield will find Campbell and Lugg's *Handbook* of much practical value. Even with the assistance of a nurse or other interpreter it is often difficult to find just the correct phrase which will elicit the required answer. Without such an assistant this book is invaluable.

Apart from the sections devoted to language difficulties, this *Handbook* offers a concise fund of information which will be of particular interest to practitioners in Natal, and to those faced with the necessity of seeing patients elsewhere and having to refer them to suitable treatment centres in Natal.

The authors' work will be greatly appreciated by all District Surgeons new to Natal, as they have provided in pocket-book size a wealth of valuable information.